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Tinidazole - a new preparation for *Trichomonas vaginalis* infections
I. Laboratory evaluation

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Tinidazole is a potent member of a new series of nitroimidazoles which are being used as antibiotics (Howes, Lynch, and Kivlin, 1970). The formula is: ethyl (2-(2-methyl-5-nitro-1-imidazolyl) ethyl) sulphone. Nothing has been published about the effect of tinidazole on strains of *Trichomonas vaginalis* isolated from clinical infections. A laboratory study of the relative efficacy of tinidazole and metronidazole against strains of *T. vaginalis* from patients and the serum level of tinidazole after its ingestion in a single dose are the subjects of this study.

Material and methods

Minimum inhibitory and minimum trichomonicidal concentrations (MIC and MCC)

These were determined essentially as described earlier (Forsgren, 1972). Eight freshly isolated strains of *T. vaginalis* taken at random from patient specimens formed the subject of the study. Before use, the organism was grown in Diamond's medium (Diamond, 1957) at 37°C. A suspension of 8×10^4 *T. vaginalis* organisms in 1 ml. thioglycolate medium was added to metronidazole and tinidazole in serial two-fold dilutions in 1 ml. saline, giving a final concentration of 4×10^4 viable organisms per ml. After incubation for 3 days at 37°C., a microscopical examination was performed, and the highest dilution of tinidazole without any motile organisms was recorded as the MIC. From each test tube 0·2 ml. was transferred to 4 ml. Diamond's medium and the subculture was incubated for 5 days. Evaluation of the trichomonicidal activity was based on the final result of the subculture and the MCC was defined as the concentration (μg./ml.) in which no viable organisms could be detected by subculture. The determinations were always carried out in duplicate.

Serum levels

The levels of tinidazole were determined on serum taken from four healthy volunteers before and at intervals after ingestion of 2 g. tinidazole on an empty stomach. The sera were heat-inactivated (Forsgren, 1972), diluted in saline, and tested against *T. vaginalis* (Milan*) in thioglycolate medium, and finally subcultures were performed in Diamond's medium as described above. The serum level was calculated by reference to a standard series of tubes containing known concentrations of tinidazole.

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Results

Table I shows the MIC values of metronidazole and tinidazole for the eight strains of *T. vaginalis* isolated from patients. The MIC values for metronidazole (0·31 to 1·25 μg./ml.) were up to four times those for tinidazole (0·12 to 1·25 μg./ml.). The mean values were 0·90 and 0·52 μg./ml. respectively.

TABLE I *Minimum inhibitory concentration (MIC) of metronidazole and tinidazole for freshly isolated strains of* T. vaginalis *determined by incubation for 3 days with* 4×10^4 *trichomonads per ml. thioglycolate medium*

Strain of T. vaginalis	*MIC (μg./ml.)*		*Percentage activity of metronidazole relative to tinidazole*
	Metronidazole	*Tinidazole*	
1	1·25	1·25	100
2	0·31	0·12	37·5
3	1·25	0·31	25
4	0·47	0·16	33
5	1·25	0·47	37·5
6	1·25	0·94	75
7	0·94	0·63	67
8	0·47	0·31	67
Mean value	0·90	0·52	57·8

As demonstrated in Table II, the differences in MCC for the two drugs were even more striking. The MCC values for metronidazole were 1·88 to 10·0 μg./ml. (mean 3·83), and for tinidazole 1·25 to 2·5 μg./ml. (mean 1·56, which is roughly 40 per cent. of that for metronidazole).

These results are in agreement with an earlier report on one laboratory strain of *T. vaginalis* (Howes and others, 1970).

The serum levels of tinidazole in four healthy volunteers, 20, 21, 22, and 23 years old, who ingested 2g. tinidazole in a single dose are shown in the Figure.

High levels (15 to 30 μg./ml.) were found after 4 hrs and the highest values (20 to 40 μg./ml.) after 6 to

TABLE II *Minimum trichomonicidal concentration (MCC) of tinidazole and metronidazole for freshly isolated strains of* T. vaginalis. *The determinations were done by incubation for* 3 *days followed by subculture for* 5 *days*

Strain of T. vaginalis	*MCC (μg./ml.)*		*Percentage activity of metronidazole relative to tinidazole*
	Metronidazole	*Tinidazole*	
1	10·0	1·25	12·5
2	2·5	1·25	50
3	2·5	1·88	75
4	2·5	1·25	50
5	5·0	1·88	37·5
6	3·75	2·5	67
7	1·88	1·25	67
8	2·5	1·25	50
Mean value	3·83	1·56	40·7

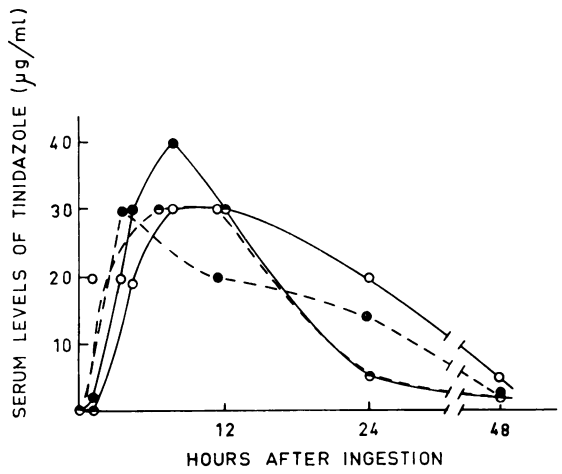

FIGURE *Serum levels of tinidazole in four healthy volunteers after ingestion of* 2 *g. in a single dose*

11 hrs. After 24 hrs, serum levels of 5 to 20 μg./ml. were still being recorded and 48 hrs after ingestion the levels were 1·88 to 5 μg./ml. Similar serum levels have been reported after ingestion of a single dose of 2 g. metronidazole (Woodcock, 1972).

Summary and conclusions

The minimum trichomonicidal concentrations of tinidazole for eight strains of *T. vaginalis* freshly isolated from patients were 1·25 to 2·5 μg./ml. (mean 1·56). For metronidazole the values were 1·88 to 10 μg./ml. (mean 3·83). Thus tinidazole had a trichomonicidal effect 1·3 to 8 times higher than that of metronidazole.

Moreover, 6 to 11 hrs after the ingestion of 2 g. tinidazole in a single dose, the highest serum levels in four healthy volunteers were 20 to 40 μg./ml.; 48 hrs after ingestion, the serum concentration of tinidazole remained higher than the minimum trichomonicidal concentration for most of the investigated strains of *T. vaginalis*.

References

DIAMOND, L. S. (1957) *J. Parasitol.*, **43,** 488

FORSGREN, A. (1972) *Brit. J. vener. Dis.*, **48,** 205

HOWES, H. L., LYNCH, J. E., and KIVLIN, J. L. (1970) 'Antimicrobial Agents and Chemotherapy—1969', ed. G. L. Hobby, p. 261. American Society for Microbiology, Bethesda, Maryland

WOODCOCK, K. R. (1972) *Brit. J. vener. Dis.*, **48,** 65

Tinidazole, une nouvelle préparation contre les infections à *Trichomonas vaginalis* I. Constations de laboratoire

SOMMAIRE

La concentration trichomonacide minimale du tinidazole pour 8 souches de *T. vaginalis* isolées récemment chez des malades se situa entre 1,25 et 2,5 μg/ml (moyenne: 1,56). Pour le métronidazole, ces valeurs se situèrent entre 1,88 et 10 μg/ml (moyenne: 3,83). Ainsi, le tinidazole a un effet trichomonacide 1,3 à 8 fois plus élevé que celui du métronidazole.

D'autre part, 6 à 11 heures après l'ingestion de 2g de tinidazole en une seule prise, les taux sériques les plus élevés pour quatre volontaires sains furent entre 20 et 40 μg/ml. 48 heures après l'ingestion, la concentration sérique de tinidazole resta plus élevée que la concentration trichomonacide minimale pour la plupart des souches de *T. vaginalis* examinées.